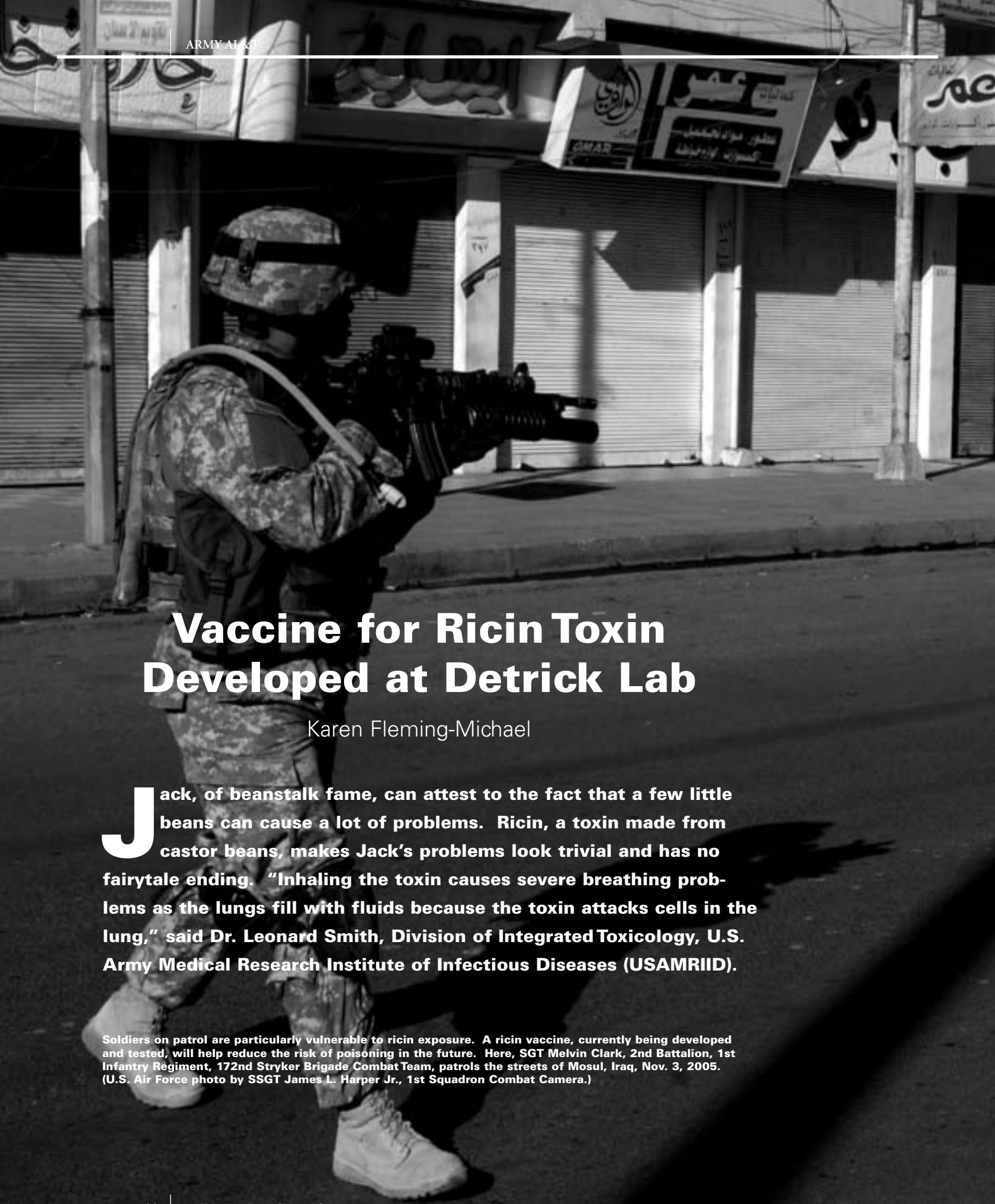

Vaccine for Ricin Toxin Developed at Detrick Lab

Karen Fleming-Michael

Jack, of beanstalk fame, can attest to the fact that a few little beans can cause a lot of problems. Ricin, a toxin made from castor beans, makes Jack's problems look trivial and has no fairytale ending. "Inhaling the toxin causes severe breathing problems as the lungs fill with fluids because the toxin attacks cells in the lung," said Dr. Leonard Smith, Division of Integrated Toxicology, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).

Soldiers on patrol are particularly vulnerable to ricin exposure. A ricin vaccine, currently being developed and tested, will help reduce the risk of poisoning in the future. Here, SGT Melvin Clark, 2nd Battalion, 1st Infantry Regiment, 172nd Stryker Brigade Combat Team, patrols the streets of Mosul, Iraq, Nov. 3, 2005. (U.S. Air Force photo by SSGT James L. Harper Jr., 1st Squadron Combat Camera.)

Ingesting ricin causes vomiting and diarrhea that may become bloody and result in dehydration, according to the Centers for Disease Control (CDC) Web site. The toxin also causes hallucinations, seizures and blood in the urine. Since 1989, Smith and other toxin experts at USAMRIID have worked on finding a vaccine to combat ricin exposure. Whether it comes through the air or deliberate contamination of the food or water supply, no antidote exists for people who have been exposed to ricin.

"It's a heck of a lot easier to protect someone with a vaccine before a ricin exposure rather than to treat them with a drug afterward," Smith said. "Once ricin gets in the cells and has done the damage, it's going to be very difficult, if not impossible, to treat someone who has been exposed to a large dose. The damage has been done by the time people know they are affected. When people start to have symptoms, it may be impossible to save them with any kind of therapy."

Ricin has had its fair share of the media spotlight in recent years. Press reports said the toxin turned up in an envelope in the mailroom that serves

MAJ Andrew Magnet, 3rd Brigade, 3rd Infantry Division surgeon (left), and MAJ John Godino, 2nd Battalion, 34th Armor Brigade gastroenterologist, discuss the delivery of medical supplies with Baqubah General Hospital's head administrator and lead surgeon. (U.S. Army photo by SSG Suzanne M. Day.)

Ricin, a toxin that causes hallucinations, lungs to fill with fluids, etc., can be used as an aerosol or to deliberately contaminate food and water supplies. Here, Master-at-Arms 2nd Class Adam Ortega inspects his bottled water supply on the Al Basrah Oil Terminal off the Iraqi coast. Ortega is assigned to Mobile Security Detachment-25. (U.S. Navy photo by PH1 Aaron Ansarov, Fleet Combat Camera.)

Sen. Bill Frist's office and a postal handling facility in Greenville, SC. It was also at the center of a plot in London where suspected al-Qaeda members were trying to make it. Listed as a category B bioterrorism agent by the CDC, ricin is a threat to both service members and the public.

"It can be obtained quite readily as a by-product of castor beans," said Smith, who has worked for USAMRIID for 24 years. "After you extract what you need from the beans, like castor oil, there's quite a bit of ricin left behind. We have no medical solutions to defend against ricin intoxication, and so we are vulnerable."

According to the CDC, ricin is also a stable substance that's not affected much by very hot or cold temperatures. Because of ricin's sinister traits, researchers at USAMRIID have been heartened by recent results they've had with their latest attempt at a vaccine. Work on a ricin vaccine began in 1989, and the quality attributes of two vaccine candidates the institute developed early on didn't meet U.S. Food and Drug Administration (FDA) expectations. The third, a recombinant vaccine, capitalized on lessons learned from the earlier attempts.

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Ricin is composed of two protein subunits, the A and B chains. When the B chain binds the toxin to a cell's surface, it permits the A chain to enter the cell. Once it's inside, the A chain stops new protein synthesis and causes cell death. In earlier attempts to develop a ricin vaccine, researchers thought that isolating the entire ricin A chain could produce immunity. But they found that the chain wasn't stable, a key element for getting a vaccine approved for use. By using molecular modeling and protein engineering, researchers — including Drs. Mark Olson, John Carra, Virginia Roxas-Duncan, Robert Wannemacher, Charles Millard and Smith — designed the new vaccine. The team started with a computer-aided analysis of the toxin structure, using a 3-D model provided by colleagues at the University of Texas-Austin.

"We compared ricin with other proteins of the same family," Olson said.

"We tried to figure out where the protein molecules are diverging within the family to see what changes were made by nature so we could make the changes we needed to make." To improve the vaccine's stability, Olson and his team modeled changes in the structure of the ricin A chain molecule. Once they predicted which genetic sequences required alterations, they handed them off to Smith and others at USAMRIID for protein engineering.

"We went straight from the computer to molecular biology," Smith said. "We had to clone and purify the proteins, and test them in animals for toxicity and protection." Four years later, the vaccine called RTA 1-33/44-198 is one the FDA should be pleased with, Smith said.

"Unlike earlier versions, this recombinant vaccine has no biological activity except for the immunity it elicits, which inactivates the toxin. It's produced and purified from E. coli and is highly stable and safe," he said.

In July 2005, researchers tested the vaccine on eight monkeys that received three shots of the vaccine over an eight-week period, then challenged them with an aerosol version of ricin. Final results of the study will be published in scientific literature later this year, but in the meantime, Smith is pleased with the results. "The bottom line is the vaccine works," he said.

Getting the vaccine into a clinical trial is the next hurdle. Currently, the USAMRIID vaccine is being considered for funding along with two other vaccines, said Andrea Atkinson, Vaccine Manager with the Joint Vaccine Acquisition Program, which manages biological defense vaccines through advanced development and FDA licensure.

Ricin is a toxin made from the beans of the castor plant. Since 1989, toxin experts at USAMRIID have worked on finding a vaccine to combat ricin exposure. (Photo courtesy of Dr. Leonard Smith.)

"We are looking at schedules, who can be licensed fastest and which one meets our requirements," Atkinson remarked, adding that the finalist for funding has not yet been selected. Once a funding stream opens up for a vaccine like ricin, many pharmaceutical companies suddenly want to put their canoe in the water, which is good news. "That's fantastic for the Soldier because you know there's always going to be something available. There's always a next-generation candidate out there," she said. "It's also risk reduction from our perspective. If we were to experience a failure with a candidate, then there's something else coming down the pipeline to mitigate that risk."

Meanwhile the USAMRIID team is developing an animal model that can be used under the FDA's animal rule to show the vaccine protects its recipients. "You can't challenge humans so it was necessary to develop a surrogate model to show the human is protected by the vaccination, especially from these products that aren't normally found in the environment," Smith said.

While funding decisions are being deliberated, Smith and his team remain busy in their Biosafety Level 2 lab looking at other funding opportunities for clinical trials and laying the foundation for them. The Defense Threat Reduction Agency has approved funding for the continued technology base development of the vaccine for FY06.

"We'll keep going. There's no question about that. My job is to try to partner with whoever we can to get resources to have a lot of vaccine made and get that clinical trial going," Smith concluded.

KAREN FLEMING-MICHAEL is a Public Affairs Officer with the U.S. Army Medical Research and Materiel Command. She has a B.A. in English literature from the University of Maryland and an M.S. in public administration from Auburn University. She has worked as an editor and public affairs specialist for 16 years.